

AMENDMENTS TO THE SPECIFICATION

Please replace the title of the application with the following new title:

METHODS FOR DETERMINING HEPATOTOXINS

Please replace paragraph number [00019], at page 5 of the specification, with the following amended paragraph:

[0019] Liver damage in patients taking acyclovir is indicated clinically by abnormal liver function tests (<http://www.hopkins-aids.edu/publications/book/ch6acyclovir.html>).

Please replace paragraph number [00023], at page 7 of the specification, with the following amended paragraph:

[0023] AY-25329, a proprietary compound, is a phenothiazine that has been shown to be toxic in liver and in kidney tissue, where it can cause nephrosis. Phenothiazines are a class of psychoactive drugs that are used to treat schizophrenia, paranoia, mania, hyperactivity in children, some forms of senility, and anxiety (<http://www.encyclopedia.com/article/new/36591.html>). Side effects associated with prolonged use of these drugs are reduced blood pressure, Parkinsonism, reduction of motor activity, and visual impairment.

Please replace paragraph number [0042], at page 11 of the specification, with the following amended paragraph:

[0042] Clofibrate has a number of effects on the rat liver, including hepatocellular hypertrophy, cellular proliferation, hepatomegaly, induction of CYP450 isozymes, and induction of palmitoyl CoA oxidation. Long term administration of clofibrate causes increased incidence of hepatocellular carcinoma, benign testicular Leydig cell tumors, and pancreatic acinar adenomas in rats. Clofibrate induces proliferation of peroxisomes in rodents and this effect, rather than genotoxic damage, is believed to be the causative event in rodent carcinogenesis (AHFS Drug Information Handbook 2001, McEvoy, ed., pp. 1735-1738; Electronic Physicians' Desk Reference-Atromid-S (clofibrate)-at ~~www.pdf.net~~; Brown and Goldstein, "Drugs used in the treatment of hyperliproteinemias," in Goodman and Gilman's The Pharmacological Basis of Therapeutics. Eighth ed., Goodman et al., eds. , pp. 874-896, Pergamon Press, New York, 1990).

Please replace paragraph number [0051], at page 14 of the specification, with the following amended paragraph:

[0051] Diflunisal, a non-steroidal anti-inflammatory drug (NSAID), is a difluorophenyl derivative of salicylic acid (Goodman & Gilman's The Pharmacological Basis of Therapeutics 9th ed., p. 631, J. G. Hardman et al., Eds. , McGraw Hill, New York, 1996). It is most frequently used in the treatment of osteoarthritis and musculoskeletal strains. NSAIDs have analgesic, antipyretic and anti-inflammatory actions, however, hepatotoxicity is known to be an adverse side effect of NSAID treatment (Masubuchi et al. (1998) JPharmacol Exp Ther 287: 208-213). Diflunisal has been shown to be less toxic than other NSAIDs, but it can eventually have deleterious effects on platelet or kidney function (Bergamo et al. (1989) Am J Nephrol 9: 460-463). Other side effects that have been associated with diflunisal treatment are diarrhea, dizziness, drowsiness, gas or heartburn, headache, nausea, vomiting, and insomnia (~~http://arthritisinsight.com/medical/meds/dolobid.html~~).

Please replace paragraph number [0071], at page 20 of the specification, with the following amended paragraph:

[0071] Thioacetamide's only significant commercial use is as a replacement for hydrogen sulfide in qualitative analyses (IARC, Vol. 7, 1974). It has also been used as a fungicide, an organic solvent in the leather, textile and paper industries, as an accelerator in the vulcanization of buna rubber, and as a stabilizer of motor fuel. The primary routes of human exposure are inhalation and skin contact with products in which thioacetamide was used as a solvent (9th Report on Carcinogens, U. S. Dept. of Health and Human Services, Public Health Service, National Toxicology Program, <http://ehp.niehs.nih.gov/toe9.html>). Thioacetamide is metabolized to a nonionic electrophile, leading to oxidative stress and other injurious events; both cytochrome P4502E1 and the flavin-containing monooxygenase system have been implicated in this bioactivation (R. Snyder & L. S. Andrews, Toxic Effects of Solvents and Vapors, in Casarett & Doull's Toxicology: The Basic Science of Poisons, Klaasen. ed., p. 737, McGraw-Hill, New York, 1996; Smith et al. (1983) Toxicol Appl Pharmacol 70: 467- 479; Jurima-Romet et al. (1993) Biochem Pharmacol 14 : 46 (12): 2163-2170).

Please replace paragraph number [0115], at page 33 of the specification, with the following amended paragraph:

[0115] The sequences of the expression marker genes of Tables 1-5WWW are in the public databases. Table 1 provides the GenBank Accession Number for each of the sequences (see www.ncbi.nlm.nih.gov/). The sequences of the genes in GenBank are expressly herein incorporated by reference in their entirety as of the filing date of this application, as are related sequences, for instance, sequences from the same gene of different lengths, variant sequences, polymorphic sequences, genomic sequences of the genes and related sequences from different species, including the human counterparts, where appropriate (see Table 3). These sequences

may be used in the methods of the invention or may be used to produce the probes and arrays of the invention. In some embodiments, the genes in Tables 1-5WW that correspond to the genes or fragments previously associated with a toxic response may be excluded from the Tables.

Please replace paragraph number [0150], at page 42 of the specification, with the following amended paragraph:

[0151] The databases of the invention may be linked to an outside or external database such as GenBank (~~www.ncbi.nlm.nih.gov/entrez/index.html~~); KEGG (~~www.genome.ad.jp/kegg~~); SPAD (~~www.grt.kyushu-u.ac.jp/spad/index.html~~); HUGO (~~www.gene-ucf.ac.uk/hugo~~); Swiss-Prot (~~www.expasy.ch/sprot~~); Prosite (~~www.expasy.ch/tools/senpsitl.html~~); OMIM (~~www.ncbi.nlm.nih.gov/omim~~); and GDB (~~www.gdb.org~~). In a preferred embodiment, as described in Tables 1-3, the external database is GenBank and the associated databases maintained by the National Center for Biotechnology Information (NCBI) (~~www.ncbi.nlm.nih.gov~~).